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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/960,708
Filing Date: September 19, 2001
Appellant(s): CRABTREE ET AL.

David C. Scherer and Bret Field
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/28/06 appealing from the Office action mailed 08/12/05 and the BPAI remand of 10/25/06.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Jiang et al. [Carcinogenesis Vol. 14 : 67-71, 1/1993]

Flanagan et al. [Nature Vol. 352 : 803-807, 8/29/1991]

The examiner refers to Bolontrade et al. [Carcinogenesis Vol. 19(12): 2107-2133, 1998] cited in applicants IDS filed 1/16/03.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8-11, 15-18, 35, 37, 39, 40, and 44 remain rejected under 35 U.S.C. 102(b) as being anticipated by Jiang et al [Carcinogenesis Vol. 14(1):67-71, 1993].

Jiang et al disclose the inhibition of tumor formation in mice comprising the administration of FK506. Jiang et al also disclose that it was known in the art that administration of cyclosprorin A, which is "remarkably similar" in biological properties with FK506, to mice inhibited skin tumor formation in mice. Jiang et al demonstrate tumor inhibition in Figure 1 via FK506 in mice with papillomas promoted by DMBA/TPA treatment, for example. The prior art methods include all the steps of the instant methods and use the same compound specifically recited in the claims and the effects [inhibiting angiogenesis/vascular development] are considered to be inherent in the prior art methods.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36-44, 46 and 47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al as applied to claims 8-11, 15-18, 35, 37-40 and 45-47 above, and further in view of Flanagan et al.

The instant claims recite the use of cyclosporine, rapamycin and synthetic mimetics and derivatives thereof in the claimed methods.

Jiang et al disclose the inhibition of tumor formation in a mouse comprising the administration of FK506 and also disclose that it was known in the art that administration of cyclosprorin A, which is "remarkably similar" in biological properties with FK506, to mice inhibited skin tumor formation in mice (see Figure 1, for example). The prior art methods include all the steps of the instant methods and the effects [inhibiting angiogenesis/vascular development] are considered to be inherent in the prior art methods. It is clear from the teachings of Jiang et al that it would be obvious to use compounds with common biological properties with FK506 in their methods since it was the common properties of FK506 to cyclosprorin A that caused them to determine the effects of FK506, for example (see page 67, for example).

It is further taught in Flanagan et al that FK506 and cyclosprorin and FK506 have similar properties as is evidenced by their interchangeable use in the methods taught therein, for example. It is further taught that rapamycin is a structural analogue of FK506 and have taught its use a control in experiments utilizing FK506, for example.

The prior art therefore clearly teaches the interchangeable use of Cyclosporin A and FK506 and rapamycin based on their biological properties which would clearly indicate to one in the art to use compounds with the specific biological properties of cyclosprorin A and FK506 in the method of Jiang et al and furthermore it is clear that one would at least utilize rapamycin as a control in the methods of Jiang et al, for example, as taught by Flanagan et al.

The invention, as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

(10) Response to Argument

Appellant argues that the Jiang reference fails to anticipate the claimed invention and first address claims 8-11, 35, 37 and 39.Appellant asserts on page 6 that the examiner asserts that the Jiang reference has inherently **demonstrated** that the anti-angiogenic activity of FK506 is effective in treating a subject with a condition with unwanted angiogenesis. Appellant description of the examiners position is not correct. The examiners position is that the prior art discloses all of the method steps of the invention. The angiogenic activity of the FK 506 in the prior art is inherent and does not need to be demonstrated since, for example, appellant has shown that FK506 functions to inhibit angiogenesis/vascular development in a subject with a condition associated with unwanted angiogenesis, it would naturally flow that the FK506 used in the methods

of the prior art function the same since it [FK506] is used as prescribed by the instant claims.

Appellant argues that Jiang fails to teach inhibition of angiogenesis in a host by administering an inhibitory agent as claimed. At page 7 of Appellants brief applicant provides an accurate summary of the Jiang et al reference, but then assert that the examiner asserts that Jiang et al. has inherently demonstrated that the anti-angiogenic activity of FK506 is what is responsible for its ability to reduce papilloma formation. The examiner offers that the Jiang reference shows that upon administration of FK506 to DMBA/TPA treated mice, papilloma formation is inhibited. The examiner does not assert that it is because of the angiogenesis inhibition properties of FK506 that the mice of Jiang have reduced papilloma formation, but the examiners asserts that the FK506 administered to the mice would indeed have the inherent property of angiogenesis/vascular development inhibition.

Appellant has raised a new argument asserting that the Jiang reference first fails to show that the papilloma formation in the disclosed mouse model system requires angiogenesis, second that the inhibition of papilloma formation by FK506 in their model is due to inhibition of angiogenesis, and third, fails to teach that the papilloma formation by FK506 in their model system is due to inhibition of Ca2+ /calcinuerin/NF-ATc.

The examiner asserts that if the reference taught all of the above there would be no need for an inherency argument. It is noted that Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art.

Appellant has raised the new argument "that the Examiner has failed to provide any extrinsic evidence to establish that papilloma formation in this mouse model requires angiogenesis (i.e., that inhibition of angiogenesis in this model will necessarily inhibit papilloma formation)." Appellant appear to want extrinsic evidence for limitations not in the claims. For example, inhibiting angiogenesis in a subject with a condition associated with unwanted angiogenesis with a Ca2+/caccineurin/NF-ATc inhibitory agent such as FK506 is all that the claim requires. Nowhere does the claimed invention require that the condition associated with unwanted angiogenesis "require angiogenesis (i.e., that inhibition of angiogenesis in this model will necessarily inhibit papilloma formation)." The claim only requires that there be inhibition of angiogenesis in a subject that has a condition that is associated with angiogenesis. Appellant then asserts that it "does not necessarily flow that agents that inhibit angiogenesis will inhibit papilloma formation in this mouse model." This assertion is extremely confusing to the examiner since Jiang has indeed shown the inhibition of papilloma formation via the administration of FK506 which according to applicant is an inhibitor of angiogenesis/vascular development.

Since Appellant has not before raised the issue of angiogenesis occurring in the model of Jiang et al the examiner wishes to make the record clear that there is indeed angiogenesis occurring in the model of Jiang et al. and furthermore would have been clearly apparent to one of ordinary skill in the art. Appellant is aware of the disclosure of Bolentrade et al. Carcinogenesis Vol. 19, No. 12 pages 2107-2113, 1998 as Appellant submitted this reference as part of and IDS on 1/16/03. Bolentrade is relied on only to

provide background to the Board on an issue not before brought before the examiner. Bolentrade et al show that angiogenesis is an early event in the development of chemically induced skin tumors. On page 2107 it is disclosed "the best studied animal cancer model with a benign exophytic stage is the mouse skin two-stage carcinogenesis model, in which tumors are induced by a single exposure to a genotoxic agent (initiation) followed by repeated exposure to a non-genotoxic tumor promoter. In mouse skin two stage carcinogenesis regimens initially induce squamous cell papillomas . . ."At page 2108 (third full paragraph) it is stated that "the angiogenesis switch in the mouse skin carcinogenesis model occurs very early in papilloma development . . ." And the last paragraph on page 2108 states "[t]he angiogenesis switch does not turn on during the progression of papillomas to malignancy: instead, it appears very early in the formation of papillomas, giving rise to well-vascularized tumors from the beginning of their histogenesis. In the first paragraph under the heading "Materials and Methods" on page 2108 it is noted that the same DMBA/TPA procedure in Jiangs' et al model is used. The entire disclosure of Bolontrade clearly shows that papillomas do indeed have angiogenesis and are at least conditions associated with unwanted vascularization. It is noted that Bolontrade also disclose that TPA administration produces a mild angiogenesis response in mouse skin in addition to a full angiogenic response during the first stages of papilloma formation (see page 2110, second column lines 19-25, for example). There is no doubt that angiogenesis occurs in the subject mice of Jiang et al.

In regard to Appellants second assertion that the examiner has failed to show that the inhibitory effect of FK506 on papilloma formation in the model of Jiang et

al is due to its antiangiogenic properties. Again, this is not even required in the claims. Furthermore the FK506 inhibits angiogenesis as demonstrated by applicant. The FK506 would clearly be expected to function as an angiogenesis/vascular development inhibitor as applicant asserts in there own specification.

Appellant then asserts that the examiner has failed to show that the papilloma formation in Jiang is due to the inhibition of Ca2+/calcinuerin/NF-ATc. Again, the claims do not require this. The claims require that angiogenesis is inhibited by such an inhibitor. Appellant identifies FK506 as just such an inhibitor. Jiang uses the same inhibior in a subject with a condition associated with unwanted angiogenesis. One would clearly expect the inhibitor of angiogenesis to function as applicant asserts it does in their specification.

Appellants' assertion that Jiang contradicts the use of Ca^{2+}/calcinuerin/NF-ATc is not clear at all. Appellant discloses and claims the use of FK506 and cyclosporin A in the methods that require an inhibitor of Ca^{2+}/calcinuerin/NF-ATc. Jiang et al disclose FK506 and cyclosporin A. Again, it is noted that inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. Jiang et al do not have to be aware of the antiangiogenic/anti-vascular development properties of these compounds. The fact is they used them in such a way as to meet all the method steps and requirements of the claimed invention.

Appellant then argues claims 15-18, 40 and 44. Appellant asserts that Jiang et al do not teach inhibition of tumor growth in a host by administering a Ca^{2+}/calcinuerin/NF-

ATc inhibitory agent as claimed. Appellant argues as though the inhibition of formation and the inhibition of growth are mutually exclusive and also seem to assert that the neoplastic disease condition and the tumor in the claims are required to be one and the same. The claims are not so limited as Appellant seems to argue. But even taking applicant position as an embodiment to be argued, Jiang et al still indeed anticipate the invention. Appellant asserts that it "does not necessarily flow that the ability of FK506 (or any agent) to inhibit papilloma formation in this mouse model ids due to inhibition of Ca^{2+}/calcinuerin/NF-ATc." The mice of Jiang et al have a neoplastic disease. The mice are administered FK506 which applicant asserts is a Ca^{2+}/calcinuerin/NF-ATc inhibitory agent. Tumor formation in the mice is inhibited. If tumor formation is inhibited it is not growing and thus growth is inhibited. Jiang et al do not need to be aware that the reason that the tumors may have been inhibited was due to the fact that the FK506 is a Ca^{2+}/calcinuerin/NF-ATc, but the fact remains that the disclose of Jiang et al meet all of the requirements of the claims.

Appellant then argues the obviousness of claims 36-44, 46 and 47.

First Appellant argues claim 36-39. Appellant asserts that there is no reasonable expectation of success that one would expect inhibition of angiogenesis with cyclosporin A or Rapamycin. The issue is not whether one would have a reasonable expectation that a cyclosporin or rapamycin would inhibit angiogenesis but whether one would have a reasonable expectation that they would function as the FK506 functioned in there experiments. It is clear that a reasonable expectation exists for this and was the basis of

the rejection of record. The fact that rapamycin and cyclosporin will function to inhibit angiogenenesis a fact shown by Appellants specification. Thus when rapamycin or cyclosporin is used in the methods of Jiang et al inhibition of angiogenesis is inherently occurring.

Appellant then argues claims 40-44 asserting that no reasonable expectation exists for inhibition of tumor growth with a Ca^{2+}/calcinuerin/NF-ATc inhibitory agent. This is confusing since Jiang et al report that cyclosporin has been shown in the prior art to tumor inhibitory properties and was indeed the reason they studied FK506. Appellant fails to address the rejections as written and argues as if one in the art must know the inhibitor has Ca^{2+}/calcinuerin/NF-ATc inhibitory properties. The use of some of such inhibitors would be obvious for the reasons set forth in the rejections of record which appellant has not addressed.

Appellant then argues claim 47. Appellant again argues as though the claim is limited to established tumor growth and as explained above the claim is not so limited. Applicant argues that one would not perform the claimed method based on the teaching of Jiang et al since Jiang et al does not provide an accurate readout of tumor growth inhibiting properties of an agent. The Rejection is based on the obviousness of using a cyclosporin in the method of Jiang et al. Jiang et al have shown that papilloma formation is inhibited with FK506 and assert that the reason they studied FK506 was indeed because of inhibition seem with cyclosporin in the prior art. If one inserted the use of cyclosporin in the methods of Jiang et al one would clearly expect an inhibition of

papillomas. Appellant own specification makes it clear that cyclosporin will inhibit tumor growth.

It is noted that Appellant arguments against Jiang et al and the scope of there own claims appear to indicate that one can expect angiogenesis inhibition and tumor growth inhibition via Ca^{2+}/calcinuerin/NF-ATc inhibitors such as FK506 in any condition other than that of the Jiang et al mice.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Primary Examiner
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Conferees:

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Communication Re: Board Remand mailed 10/25/06.

Attached is a revised Examiners Answer that contains a corrected "Evidence Relied Upon" section.

Also attached is a signed and initialed copy of form PTO/SB/08A filed 1/16/03.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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